SIU SCHOOL of MEDICINE

Overview of Potential Agents of Biological Terrorism

During the Great Depression, Hans Zinsser, a bacteriologist and historian wrote that "Infectious Disease is one of the few genuine adventures left in the world."

"Infectious Disease is one of the great tragedies of living things - the struggle for existence between different forms of life . . Incessantly the pitiless war goes on, without quarter or armistice - a nationalism of species against species." Hans Zinsser- Rats, Lice and History (1934)

Infectious Agents as Tools of Mass Casualties

Historically, outbreaks (wars) of microbial species against the human species have killed far more people than war itself. Examples include i) killing of 95% of Pre-Columbian Native American populations by diseases like small pox, measles, plague, typhoid and influenza; ii) death of 25 million Europeans (a quarter of the

population) caused by Bubonic Plague in the 14th century and 21 million deaths due to the influenza pandemic of 1918-1919 (1).Worldwide, naturally occurring infectious diseases remain the major causes of death. In the United States, the impact of a number of very virulent biological agents and/or their toxins has been drastically reduced because of a very accessible health care system and excellent public health infrastructure. Still, a substantial number of people (approximately 70,000) die each year from infectious diseases (2). The travel and trade necessary for economic globalization, continued potential for transmission of infectious agents from animals to humans, and large populations living in proximity in major urban areas of the world, make disease outbreaks a major threat. The resistance of common pathogens to the available antimicrobial agents adds significantly to the threat. Advances in public health, diagnostic and pharmacological interventions are needed to protect the population from emerging and re-emerging infectious diseases. The global nature of infectious disease threats is well described in a statement prepared by Dr. David L. Heymann, Executive Director for Communicable Diseases, World Health Organization. This statement was presented to the Committee on Foreign Relations, United States Senate, during a hearing on "The Threat of Bioterrorism and the Spread of Infectious Diseases" on September 5, 2001 (3).

Bioterrorism , National Security and Law

Bioterrorism has now been defined as the intentional use of a pathogen or biological product to cause harm to a human, animal, plant or other living organisms to influence the conduct of government or to intimidate or coerce a civilian population(4). Biological agents are easy to develop as weapons, are more lethal than chemical weapons, are less expensive and more difficult to detect than nuclear weapons (5). Diseases caused by biological agents are not only a public health issue but also a problem of national security. Two simulated biological attacks, Dark Winter (small pox) and TOPOFF (plague), in the United States demonstrated serious weaknesses in the public health system that could prevent an effective response to bioterrorism or severe naturally occurring infectious diseases (6,7,8,9,10). The intentional dispersal of anthrax through the United States Postal Service that followed the terrorist attacks of September 11, 2001, brought these issues into a clear focus. The United States government began a process to strengthen the public health infrastructure. The need for law reform was recognized as law has long been considered as an important tool of public health (11). The power to act to preserve the Public's Health is constitutionally reserved primarily to the states as an exercise of their police powers. Some states like Colorado and Rhode Island had developed legislation or administrative public health plans for a bioterrorism event prior to September 1, 2001. The Model Act was designed to update and modernize the state public statutes and to avoid problems of inconsistency, inadequacy and obsolescence. The Model State Emergency Health Powers Act (MSEHPA or Model Act) was drafted by the Center for Law and the Public's Health at Georgetown and Johns Hopkins Universities at the request of the Centers for Disease Control and Prevention (CDC) and in collaboration with members of national organizations representing governors, legislators, attorneys general and health commissioners (4,12). This act provides state actors with the powers to detect and contain bioterrorism or a naturally occurring disease outbreak. The Model Act is structured to facilitate five basic public health functions i) Preparedness,

comprehensive planning for a Public Health emergency; ii) Surveillance, measures to detect and track Public Health emergencies; iii) Management of Property, ensuring adequate availability of vaccines, pharmaceuticals and hospitals as well as providing power to abate hazards to the Public's Health; iv) Protection of Persons, powers to compel vaccination, testing, treatment, isolation and quarantine when clearly necessary; and v) Communication, providing clear and authoritative information to the public. The act also contains a modernized, extensive set of principles and requirements to safeguard personal rights. Based on MSEHPA, legislative bills have been introduced in 34 states and the District of Columbia. As of June 26, 2002, 16 states and the District of Columbia already have enacted a version of the act and the states enacting or expected shortly to enact legislation, influenced by the Model Act were Arizona, Florida, Georgia, Hawaii, Maine, Maryland, Minnesota, Missouri, New Hampshire, New Mexico, Oklahoma, South Carolina, South Dakota, Tennessee, Utah and Virginia.
The Model State Emergency Health Powers Act (MSEHPA)
Reprinted *JAMA*, August 7, 2002, Vol 288 No. 5 Page 625-628

A critique of the Model State Emergency Health Powers Act was published by Annas G. In Bioterrorism, Public Health and Civil Liberties. NEJM, 2002 April 24:346(13) At the federal level, Public Health Security and Bioterrorism Preparedness and Response Act of 2002, HR 3448, was passed by the United States Congress on May 23, 2002 and signed into law (Public Law 107-188) June 12, 2002. The bill is intended to improve the health system's ability to respond to bioterrorism, protect the nation's food supply and drinking water from bioterrorist attacks, speed the development and production of new drug treatments and vaccines, address shortages of specific types of health professions, improve coordination of federal anti-bioterrorism activities, increase investment in federal, state, and local preparedness and expand controls over the most dangerous biological agents and toxins. The American Society for Microbiology (ASM) has testified before congress on issues surrounding biosecurity and has worked closely with congress in the drafting of Title II to balance Public Health concern over safely and security with need to protect legitimate scientific research and diagnostic testing. Important new provisions for the possession, use and transfer of select agents, (42 biological agents and toxins listed in Appendix A of 42 CFR part 72), are included in Title II of HR 3448, Enhancing Controls on Dangerous Biological Agents and Toxins. On July 12, 2002, the CDC announced preliminary guidance for notification of possession of select agents as mandated in Section 202 (a) of Public Law 107-188, the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (Appendix B). The notice states that each facility should designate a responsible facility official (RFO) to complete the notification of possession form by September 10, 2002. The RFO will need to inventory the facility and consult with others (e.g. Principal Investigators) to obtain the required information. At our institution a Designated Safety Officer in collaboration with the Infection Control and Safety Committee address these issues. In order to avoid inconsistencies and noncompliance, at the July meeting, it was recommended to the Committee that the Principal Investigators provide a complete list of all the biological agents being used in their laboratories. The Safety Officer would then use the information needed to register with the Secretary of Health and Human Services and provide inspections to ensure safety and compliance with the requirements.

Historical Perspective and Trends Related to Bioterrorism

The intentional use of living organisms or infected materials derived from them has occurred over centuries during war and "peace" time by armies, states, groups and individuals (14,15,16). One of the first recorded uses of a biological agent in the war was in 184 BC. The Carthaginian soldiers led by Hannibal used snakes in the battle against King Eumenes of Perganium and achieved a victory (17,18). As early as 300 BC, the Greeks polluted the wells and drinking water supplies of their enemies with animal corpses. The use of catapults and siege machines introduced new technology to biological warfare. Some of the more recent events of biological warfare are chronicled below -

- The Tartars catapulted bodies infected with plague into Caffa (now Ukraine) in 1346 at the end of a 3 day siege.
- The inhabitants of Central and South America were decimated by small pox and measles that accompanied the Spanish conquistadors.
- British forces used blankets contaminated with small pox to infect North American Indians in the 18th century.
- The modern era of biological weapons development began immediately before and during World War II. The Japanese released fleas infected with plague in Chinese cities in the 1930's and 1940's. Between 1940 and 1942 Japanese unit 731 dropped bombs containing up to 15 million plague infected fleas on two Chinese cities - Quxian and Ning-hsien, resulting in at least 120 deaths. Water supplies and food items were contaminated with B. anthracis, V. Cholera, Shigella spp., Salmonella and Yersinia pestis.
- Weather Underground (1970), a United States revolutionary group intended to obtain agents at Ft. Detrick by blackmail and to temporarily incapacitate United States cities to demonstrate the impotence of the federal government. Report originated with a US Customs informant.
- R.I.S.E. (1972). College students influenced by ecoterrorist idealogy and 1960's drug culture planned on using agents of typhoid fever, diphtheria, dysentery and meningitis to target the entire world population initially and later narrowed the plan to five cities near Chicago. The attack was aborted when cultures were discarded.
- Bulgarian defector Georgi Markov was assassinated in Lauda (1978) using ricin-filled pellet infected with a spring-loaded device disguised in an umbrella. Similar device used against a second defector in the same area was unsuccessful.
- Sverdlovsk, Russia (1979). Accidental release of anthrax from Soviet bioweapons facility caused an epidemic of inhalational anthrax with at least 77 cases and 60 deaths.
- Red Army Faction (1980). Members of a Marxist revolutionary ideology group allegedly cultivated botulinum toxin in a Paris safe-house and planned attacks against at least 9 German officials and civilian leaders. This probably was an erroneous report, later repudiated by the German government.
- Rajneeshee Cult (1984). Indian religious cult headed by Rajneeshee plotted to contaminate restaurant salad bars with Salmonella typhimanice in Dallas, Oregon. The motivation was to incapacitate voters to

win local elections and seize political control of the county. The incident resulted in a large community outbreak of salmonellosis involving 751 patients and at least 45 hospitalizations. The plot was revealed when the cult collapsed and members turned informants.

- Minnesota Patriots Council (1991). Right wing "Patriot" movement obtained Ricin extracted from castor beans by mail order. They planned to deliver ricin through skin with DMSO and aloe vera or as dry aerosol against IRS officials, US Deputy Marshals and local law enforcement officials. Group was penetrated by Federal Bureau of Investigation (FBI) informants.
- Aum Shinrikyo (1995). New Age Doomsday cult seeking to establish a theocratic state in Japan attempted at least 10 times to use anthrax, botulinum toxin, Q fever agent and Ebola virus in aerosol form. All attempts with biological weapons failed. Multiple chemical weapon attacks with Sarin, Vx, hydrogen cyanide in Matsumato, Tokyo and an assassination campaign were conducted. Nerve gas Sarin killed 12 and injured 5500 in Tokyo subway.
- Texas (1997). Intentional contamination of muffins and donuts with laboratory cultures of Shigella dysenteriae. The event caused gastroenteritis in 45 laboratory workers and 4 were hospitalized.
- Larry Wayne Harris (1998). Allegedly threatened to release "military grade anthrax" in Las Vegas, Nevada. Obtained plague and anthrax (vaccine strains), repeatedly isolated several other bacteria. Made vague threats against US federal officials on behalf of right wing "patriot" groups. Arrested when he talked openly about biological weapons terrorism.
- Unknown individual/group (2001). Intentional dissemination of anthrax spores through the US Postal System leading to the death of five people, infection of 22 others and contamination of several government buildings. Investigation into the attacks so far has not led to any conclusions.

Chronology of Anti-Bioterrorism (Biosafety) Actions (19).

1910 - 1920's	The fist use of chemical and biological weapons in combat leads to efforts to ban their use.
1925	The Geneva Protocol prohibits the use of biological and chemical weapons in war. The United States signs but fails to ratify the treaty. The treaty contained no provision for verifications and inspection.
1950's - 1970's	The Soviet Union and United States build arsenals of biological and chemical weapons. International pressures mount to draw up new treaties to curb such weapons.
November	President Richard M. Nixon unilaterally renounces the use of biological weapons

25, 1969	in war by the United States and restricts research to immunization and safety efforts. Three months later, he extends the ban to include toxins.
1972	Convention on the prohibition of the development, production, and stockpiling of bacteriological (biological) and toxin weapons and their destruction opened for signature at Washington, London, and Moscow on April 10, 1972.
1975	The United States ratifies the Biological and Toxin Weapons Convention as well as the 1925 Geneva Protocol on January 22, 1975. The Biological and Toxin weapons Convention entered into force March 26, 1975. There are now 143 states parties to the convention and an additional 18 signatories (20). Article VI of the Convention that provides for actions against noncompliance has proved to be an inadequate mechanism.
1980's	Arms control initiatives fail to curb biological and chemical weapons proliferation.
1984	The Reagan administration presented a draft treaty to ban the production and storage of chemical weapons to the Conference on Disarmament in Geneva.
1990's	Concerns over exposure to chemical and biological weapons during the Persian Gulf War increased support for international treaties.
May 13, 1991	Shortly after the Allied victory against Iraq, President George Bush announced that the United States will renounce the use of chemical weapons for any reason . . . an international treaty banning them takes effect.
April, 1992	Russian President Boris N. Yeltsin declares that Russia's biological weapons program is being discontinued..
January, 1993	President George Bush signs the Chemical Weapons treaty at the convention banning the production and use of chemical weapons.
January 7, 1997	The Presidential Advisory Committee on Gulf War Veterans' illnesses, finds no conclusive evidence linking Gulf War Syndrome to exposure to chemical or biological weapons.

April 15, 1997	New regulations aimed at limiting access to chemicals and pathogens that could be made into weapons go into effect under the 1996 Antiterrorism and Effective Death Penalty Act.
April 29, 1997	The Chemical Weapons Convention went into effect. It has more than 160 signatories and 65 ratifications.
July 25, 2001	The United States rejected a protocol to strengthen the Biological Weapons Convention as well as the whole approach to it (21). Like the Chemical Weapons Conventions (CWC), a strong bioweapons protocol could add to the deterrence of bioweapons which are a much greater threat.
November 19, 2001	Fifth BWC Review Conference

Potential Biological Weapons Threat Repositories and Sources

The origin of the biological weapons program of the former Soviet Union dates back to statements by Lenin. Although experimental work was started in the late 1920's, the modern era was ushered in only with the postwar military building programs (22). The Allied Biological Weapons program had shifted from the British research into anthrax (and the development of the World War II anthrax cattlecake retaliation weapon), to a large United States based research, development and production capability. The United States military had accepted seven types of classified agents and could produce 650 tons of an agent per month at plants such as the one at Pine Bluff in Arkansas. This offensive program was unilaterally abandoned in 1969, giving impetus to the creation of the Biological and Toxin Weapons Convention. The Soviet Union signed the Convention at its inception in 1972. Unfortunately, the number of countries engaged in biological weapons experimentation has grown from 4 in the 1960's to 11 in the 1990's (23). It is estimated that at least 10 nations and possibly 17 possess biological warfare agents (24) . Of the seven countries listed by the United States Department of State as sponsoring international terrorism, at least five are suspected to have biological warfare programs (25). Nations and dissident groups have the access to skills needed to selectively cultivate some of the most dangerous pathogens and to deploy them as agents of biological terrorism and war (26).

The Japanese cult Aum Shinrikyo that released the nerve gas Sarin in the Tokyo subway also had plans for biological terrorism (27). They were in possession of large quantities of nutrient media, botulinum toxin, anthrax cultures and drove aircraft equipped with spray tanks. Members of this group had traveled to Zaire in 1992 to obtain samples of Ebola virus. Aum Shinrikyo is an example of a large well financed organization that was

attempting to develop biological weapons capability. Such organizations would be expected to cause the greatest harm, because of their access to scientific expertise, biological agents and most importantly, dissemination technology (28).

Smaller, less sophisticated organizations may use biological agents to further their specific goals rather than to kill. Such organizations could use readily available pathogens. The Rajhneeshees who attempted to influence local elections in Dallas, Oregon by contaminating salad bars with *Salmonella typhimurium* .

The third type are smaller groups or individuals who may have very limited targets, e.g. individuals or buildings. The likelihood of events related to such use is high but the public health consequences are low. As of now, the use of anthrax spores through the United States postal system seems to be an example of this type of biological terrorism. Iraq's biological weapons program dates back to at least 1974 and has been carried out secretly after the Biological and Toxin Weapons Convention had been signed. In 1995, Iraq confirmed that it had produced and deployed bombs, rockets and aircraft spray tanks containing Bacillus anthracis and botulinum toxin (29). In 1973 and 1974, the Soviet Politburo formed the organization known most recently as Biopreparat designed to carry out offensive biological weapons programs concealed behind civil biotechnology research (22). Concepts of use had been developed for each of the biological agents formally accepted by the army. In January 1991, the first ever visit to Biopreparat facilities was undertaken by a Joint United Kingdom/United States technical team. By the mid 1990's substantial changes took place within Biopreparat and a concerted effort is underway to help the Russians civilianize these former biological weapons research and development establishments. The current capability of the old Russian Ministry of Defense sites remains largely unknown. The status of one of Russia's largest and most sophisticated former bioweapons facilities, called Vector in Koltsovo, Novosibirsk is of concern. The facility housed the small pox virus as well as work on Ebola, Marburg and the hemorrhagic fever viruses (e.g., Machupo and Crimean-Congo) (26). A visit in 1997 found a half-empty facility protected by a handful of guards. No one is clear where the scientists have gone. The confidence that this is the only storage site for small pox outside the Centers for Diseases Control and Prevention is lacking.

The Threat of Biological Weapons

The Biological weapons system is comprised of four components; a payload, munition, delivery system and dispersion system. The payload is the biological agent itself. The munition protects and carries the payload to maintain its potency during delivery. The delivery system can be a missile, vehicle (aircraft, boat, automobile or truck), or an artillery shell. The dispersion system ensures dissemination of the payload at the target site. Potential methods of dispersion are aerosol sprays, explosives, and food or water contamination. Aerosol sprays are the most effective means of widespread dissemination. Depending on atmospheric conditions and the agent itself, infectious material could travel several hundred kilometers in a particle size that upon inhalation would be delivered to the terminal airways. However factors like particle size of the agent, stability of the agent under desiccating conditions and ultraviolet light, wind speed, wind direction, and atmospheric stability can alter

the effectiveness of a given delivery system. Explosions are likely to inactivate biological agents and therefore are not very effective in disseminating infectious materials. Contamination of water supplies generally requires an addition of an unrealistically large amount of biological agent(s) to a city supply. The agents may be introduced into smaller reservoirs or into the water supply after the water passes through its purification facility. Food supplies are easier to contaminate than water supplies. The outbreaks from food source may be dismissed as a "natural" event early during a bioterrorism attack (30, 31).

For a biological weapon to be highly effective, three conditions should be optimized. The biological agent should consistently produce the desired effect of death or disease. It should be highly contagious with short and predictable incubation period and infective in low doses. The disease should be difficult to identify and be suspected as an act of bioterrorism. The agents should be suitable for mass production, storage, weaponisation, and stable during dissemination. The target population should have little or no immunity and little or no access to treatment. The terrorist should have means to protect or treat their own forces and population against the infectious agents or the toxins (32).

The agents with potential of biological terrorism include bacterial, fungal and viral pathogens and toxins produced by living organisms. Infectious agents that could potentially be used include those causing anthrax (*Bacillus anthracis*), plague (*Yersinia pestis*), tularemia (*Francisella tularensis*), equine encephalitides (e.g. Venezuelan equine encephalitis viruses), hemorrhagic fevers (arenaviruses, filoviruses, flaviviruses, and bunyaviruses), and small pox (variola virus). Toxins include botulinum toxin from *Clostridium botulinum*; ricin toxin from the castor bean *Ricinus communis*; trichothecene mycotoxins from *Fusarium, Myrotecium Trichoderma, Stachybotrys*, and other filamentous fungi; staphylococcal enterotoxins from Staphylococcus aureus; and toxins from marine organisms such as dinoflagellates, shellfish, and blue-green algae. Depending on the agents, a lethal or incapacitating outcome can occur. In a military context, incapacitating agents may be more effective because the unit will not be able to perform their mission and casualties will consume scarce medical and evacuation assets (31).

Biological weapons are very attractive to the terrorist because of several characteristics. Aerosols of biological agents are invisible, silent, odorless, tasteless, and are relatively easily dispersed. They are 600 - 2000 times cheaper than other weapons of mass destruction. It is estimated that the cost would be about 0.05% the cost of a conventional weapon to produce similar numbers of mass casualties per square kilometer. The production is relatively easy, using the common technology available for the production of some antibiotics, vaccines, foods, and beverages. The delivery systems such as spray devices from an airplane, boat or car are commonly available. The natural lead time provided by the organism's incubation period (3 to 7 days for most potential organisms) would allow for the terrorists' escape before any investigation starts. In addition, the use of an endemic infectious agent may cause confusion because of the inability to differentiate a biological warfare attack from a natural epidemic. For some agents potential exists for secondary or tertiary transmission by person-to-person transmission or natural vectors.

The consequences of biological weapons use are many. They can rapidly produce mass effect that

overwhelms services and the health care system of the communities. Most of the civilian population is susceptible to infections caused by these agents. They are associated with high morbidity and mortality rates. The resulting illness is usually difficult to diagnose and treat early, particularly in areas where the disease is rarely seen. One kilogram of anthrax powder has the capability to kill up to 100,000 people depending on the mechanism of delivery (33). The economic impact of a biological attack has been estimated to be from 478 million/100,000 persons exposed (brucellosis scenario) to 26.2 billion/100,000 persons exposed (anthrax scenario) (34).

Types of Bioterrorism Attacks

A bioterrorist attack may occur in 2 scenarios - overt and covert. In the past emergency responses were prepared based on overt attacks like bombings and chemical agents that cause immediate and obvious effects. However, attacks with biological agents are more likely to be covert. They pose different challenges and require emergency planning with the involvement of the public health infrastructure. The attack by a biological agent will not have an immediate impact because of the delay between exposure and onset of illness (i.e., the incubation period). Therefore, the first victims of a bioterrorism action will need to be identified by physicians or other primary health care providers. Based on the first wave of victims, pubic health officials will need to determine that an attack has occurred, identify the organism and prevent more casualties through prevention strategies (e.g. mass vaccination, prophylactic treatment) and infection control procedures (35). The clues to a potential bioterrorist attack include an outbreak of a rare or new disease, an outbreak of diseases in a non-endemic area, a seasonal disease during an off season time, a known pathogen with unusual resistance or unusual epidemiologic features, an unusual clinical presentation or age distribution, a genetically identical pathogen emerging rapidly in different geographical areas (36).

Agents of Bioterrorism Attacks

Based on the ease of transmission, severity of morbidity, mortality, and likelihood of use, biological agents can be classified into 3 categories (Table 1) (35). Table 2 summarizes the biological agents in category A.

Table 1

Table 2

Category A Agents

Category A includes the highest priority agents that pose a risk to national security because of the following features -

i). They can be easily disseminated or transmitted person-to-person causing secondary and tertiary cases.
ii) They cause high mortality with potential for major public health impact including the impact on health care facilities.
iii) They may cause public panic and social disruption.
iv) They require special action for public health preparedness.
Anthrax, Botulism, Tularemia, small pox and viral hemorrhagic fever will be discussed in detail during the workshop. In addition, we will have two general presentations - one on laboratory diagnosis of biological weapons and the other the care of children in the event of biological terrorism.

In this presentation, I will discuss Plague as a disease and *Yersinia pestis* as a potential agent of bioterrorism followed by and overview of Category B and Category C weapons.

Plague

Microbiology and Epidemiology

Plague is caused by *Yersinia pestis*, previously called *Pasturella pestis. Yersinia pestis* is a nonmotile, nonsporulating, bipolar-staining, gram-negative coccobacillus in the genus *Yersinia* and the family Enterobacteriaceae. It is microaerophilic, indole, oxidase- and urease-negative; non-lactose fermenting and biochemically unreactive. It grows aerobically on most culture media, including blood agar and MacConkey agar. Plague is a notorious cause of catastrophic epidemics. Epidemic bubonic plague was vividly described in biblical and medieval times. This disease was estimated to have killed one fourth of Europe's population in the Middle Ages. The most recent pandemic originated in China and spread worldwide at the turn of the 20th century. Large outbreaks of pneumonic plague occurred in Manchuria and India during 1910 - 1911, and 1920 and 1921. During World War II, Japan investigated the use of plague as a biological weapon. The United States studied *Y. pestis* as a potential agent in the 1950's before the offensive BW program was terminated, and other countries have been suspected of weaponizing plague.

Clinical Features

Y. pestis is maintained in nature as a zoonotic infection in rodent hosts and their fleas in large areas of Asia, Africa and the Americas. Transmission to humans occurs by contact with fleas and respiratory droplets from animals or infected humans. In naturally occurring plague, the bite by an infected flea leads to the inoculation of thousands of organisms into a patient's skin. The bacteria migrate through cutaneous lymphatics to regional lymph nodes where they are phagocytosed but not killed. They rapidly multiply in the lymph nodes with subsequent bacteremia, septicemia, and endotoxemia that can lead quickly to shock, disseminated intravascular coagulation, and coma.

The three major forms of *Y. Pestis* infection in humans are classical bubonic plague, primary septicemic plague

and pneumonic plague, accounting for 84, 13 and 2% respectively, of cases reported in the United States from, 1947 to 1996 (37). Patients typically develop symptoms of bubonic plague 2 to 8 days after an infected flea bite. Systemic symptoms include fever, chills, weakness, and headache followed by the development of an acutely swollen lymph node or bubo within a day. The painful bubo commonly develops in the groin, axilla or cervical region and the overlying skin is erythematous. They are extremely tender, nonfluctuant, and warm with surrounding edema but no lymphangitis.

A distinctive feature of plague, in addition to the bubo, is the propensity of the disease to overwhelm the patient with a massive growth of bacteria in the blood. In the early acute stages of bubonic plague, all patients probably have intermittent bacteremia. Occasionally in the pathogenesis of plague infection, bacteria are inoculated and proliferate in the body without producing a bubo. Patients become ill with fever and actually die with bacteremia but without detectable lymphadenitis. This syndrome has been termed Primary Septicemic Plague to denote plague without a bubo. Septicemia can also occur secondary to bubonic plague. Septicemic plague leads to disseminated intravascular coagulation, necrosis of small vessels, and purpuric skin lesions. Gangrene of acral regions such as the digits and nose may also occur in advanced disease. This clinical presentation is believed to be responsible for the name "black death" in the second plague pandemic.

Primary pneumonic plague resulting from the inhalation of plague bacilli occurs rarely in the United States. Reports of two recent cases of primary pneumonic plague, contracted after handling cats with pneumonic plague, reveal that both patients had respiratory symptoms as well as prominent gastrointestinal symptoms including nausea, vomiting, abdominal pain, and diarrhea. Both patients died because of delayed diagnosis and treatment (38,39).

Secondary pneumonic plague develops in a minority of patients with bubonic or primary septicemic plague - about 12% of total cases in the United States over the past 50 years (40). The infection reaches the lungs by hematogenous spread of bacteria from the bubo. In addition to the high mortality rate, plague pneumonia is highly contagious by airborne transmission. It manifests in the setting of fever and lymphadenopathy with cough, chest pain, and often hemoptysis. Radiographically, there is patchy bronchopneumonia, cavities, or confluent consolidation (32). The sputum is usually purulent and contains plague bacilli.

The epidemiology, pathogenesis and clinical manifestations of plague following a biological attack may be different than naturally occurring plague. Primary pneumonic plague due to inhaled aerosolized *Y. pestis* bacilli would be most likely. The time from exposure to aerosolized *Y. pestis* to the development of the first symptoms in humans and nonhuman primates has been found to 1 to 6 days. The first signs of illness would be fever with cough and dyspnea, sometimes with the production of bloody, watery purulent sputum. Prominent gastrointestinal symptoms, including nausea, vomiting, abdominal pain, and diarrhea, might be present adding to diagnostic difficulty (37). The absence of buboes would differentiate primary from secondary pneumonic plague. Patients diagnosed with pneumonic plague should be housed under respiratory droplet precautions. Additionally, standard cleaning and disinfection guidelines should be followed for objects and clothing contaminated with the blood and body fluids.

Laboratory Diagnosis

A high index of clinical suspicion and a careful clinical and epidemiologic history and physical examination are required to allow timely diagnosis of plague. When plague is suspected, specimens should be obtained promptly for microbiological studies and specific antimicrobial therapy should be initiated pending confirmation. Appropriate diagnostic specimens for smear and culture include blood in all patients, lymph node aspirates in those with suspected buboes, sputum samples or tracheal aspirates in those with suspected pneumonic plagues, and cerebrospinal fluid in those with suspected meningitis. If possible, the specimens should also be examined using direct flourescent antibody (DFA) testing. An acute phase serum should be collected for *Y. pestis* antibody testing, followed by a convalescent phase specimen collected 3 to 4 weeks later.

For the Level A laboratory at a community hospital, the presence of small gram-negative coccobacilli with a safety pin appearance (seen more clearly on Wright-Giemsa rather than gram stain) from blood, lymph node aspirate or respiratory secretions from a patient with a short history of fever and lymphadenopathy should raise the suspicion of *Y. pestis.* The specimen should be submitted to the nearest Level B or C laboratory (36). Cultures demonstrate growth at 24 - 48 hours of incubation at 37OC. Automated or semiautomated systems may misidentify *Y. pestis* and laboratories without automated systems may take 4 - 6 days to suspect the organism. At the Level B laboratories, identification can be confirmed by a direct fluorescent antibody test to detect the fraction 1 (F1) envelope antigen of *Y. pestis*. This antigen is expressed only at 37OC after 24 to 48 hours incubation. These laboratories can do in vitro antimicrobial susceptibility testing by e-test, complete biochemical confirmation and specific phase lysis tests for *Y. pestis*. Enzyme immunoassay, passive hemagglutination and passive hemagglutination inhibition tests can be done to detect antibody to F1 antigen. Rapid diagnostic tests like antigen detection, IgM enzyme immunoassay, immunostaining and polymerase chain reaction are available only at some state health departments, CDC and the military laboratories.

Antimicrobial Therapy.

There is a lack of clinical trials in treating plague in humans for a number of reasons including the requirement for a large number of patients. The working group on Civilian Biodefense has made recommendations based on the best available evidence in collaboration with scientists from a number of federal agencies (37). Primary pulmonary plague during the past 50 years in the United States has had a fatality rate of 57%. The fatality rate is extremely high when treatment is delayed more than 24 hours after symptom onset. Streptomycin is the FDA approved antibiotic for plague and is responsible for reducing overall plague mortality to 5 to 14%. Gentamicin is an acceptable alternative. Gentamicin is more widely available than streptomycin and has shown equal or better activity in in vitro and in animal studies.

Tetracycline and doxycycline are also FDA approved for treatment and prophylaxis of plague. In vitro activity of tetracycline and doxycycline against Y. pestis is equivalent to that of aminoglycosides. Experimental murine models have yielded data difficult to extrapolate to humans. F1 deficient variants have decreased susceptibility to doxycycline. There are no controlled clinical trials comparing tetracycline or doxycycline to aminoglycosides

in the treatment of plague. The working group recommends that the tetracycline class of antibiotics be used to treat pneumonic plague if aminoglycosides cannot be used. Doxycycline should be considered pharmacologically superior to other agents in the class. Fluoroquinolones have demonstrated efficacy in animal studies and in vitro studies comparable to that of aminoglycosides and tetracyclines. Chloramphenicol has been recommended for treatment of plague meningitis but no clinical trials have been done. Trimethoprin/Sulfamethoxacole has been considered a second tier choice while others have recommended sulfonamides only for pediatric prophylaxis. Rifampin, Aztreonam, Ceftazidime, Cefotetan and Cefazolin have shown poor efficacy in animal studies. Resistance of Y. pestis to tetracycline class of drugs has been reported recently and Russian scientists have published a report of quinolone resistance. A multidrug resistant strain (plasmid mediated) was isolated in Madagascar (42).

Post Exposure Prophylaxis

Close contact for purposes of initiating antimicrobial prophylaxis is defined as contact with a patient at less than 2 meters. Asymptomatic persons having close household, hospital or other close contact should receive post exposure prophylaxis for 7 days. Tetracycline, doxycycline, sulfonamides and chloramphenicol have each been used or recommended for prophylaxis in this setting. The working group recommends doxycycline as the first choice for post exposure prophylaxis.

Vaccination

A licensed killed whole cell vaccine was available in the United States from 1946 to late 1998. It offered protection against bubonic plague but did not prevent or ameliorate the development of primary pneumonic plague (43). Currently, a fusion protein vaccine (F1-V antigen) is in development at the United States Army Medical Research Institute of Infectious Diseases (44). It protected mice against an inhalational challenge for a year and is now being tested in primates.

Infection Control Procedures

Standard precautions should be used for bubonic plague patients. Suspected pneumonic plague cases require strict isolation with droplet precautions for 48 hours or longer after antibiotics are started or until sputum cultures are negative in confirmed cases. Pneumonic plague transmission was prevented in close contacts by wearing masks (37,44). In addition to a surgical mask, gown, gloves and eye protection are recommended for contact with a case of pneumonic plague. Patients being transported should also wear surgical masks. Patients can be cohorted while undergoing antibiotic therapy. Isolation of close contacts refusing antibiotic prophylaxis is not recommended. Hospital rooms of patients with pneumonic plague should receive terminal cleaning and contaminated clothing should be disinfected per hospital protocol (46). Bodies of patients who have died with plague should be handled with routine strict precautions (46). If aerosol generating procedures are necessary, high efficiency particulate air filtered masks and negative pressure rooms should be used. Microbiology laboratory personnel should be alerted when a diagnosis of plague is suspected. Routine microbiology procedures should be conducted at biosafety Level 2 conditions. For activities involving high potential for

aerosol or droplet production (centrifugation, grinding, vigorous shaking and animal studies) biosafety Level 3 condition are necessary.

Y. pestis is far more susceptible to environmental conditions than sporulating bacteria such as *Bacillus anthracis*. It is very sensitive to sunlight and heat and does not survive long outside the host. In the worst case scenario analyzed by WHO, a plague aerosol was estimated to be effective and infectious for as long as 1 hour. In the setting of a terrorist release of *Y. pestis*, the aerosol would have dissipated long before the first case of pneumonic plague is recognized. Thus, there is no need for environmental decontamination of an area exposed to an aerosol of *Y. pestis*.

If vectors (fleas) and reservoirs (rodents) are present, measures must be taken to prevent the natural cycles for *Y. pestis*. Rodent control measures, flea insecticides and flea barriers for patient care areas are recommended.

Category B Agents

This category (47) contains the second highest priority agents because they
a. are moderately easy to disseminate
b. cause moderate morbidity and low mortality
c. require specific enhancement of CDC's diagnostic capacity and enhanced disease surveillance

Table 3 - Category B Bioterrorism Agents

Bacteria	Viruses	Toxins
Coxiella burnetti (Q fever) *Brucella species* (Brucellosis) *Burkholderia mallei* (Glanders) *Burkholderia pseudomallei* (Melioidosis) *Rickettsia promazekii* (Typhus fever) *Chlamydia psittaci* (Psittacosis)	Alpha viruses Venezuelan encephalomyelitis Eastern equine encephalomyelitis Westerm equine encephalomyelitis	Ricin toxin (Ricinus communis) Epsilon toxin (Clostridium perfringens) Enterotoxin B (Staphylococccus aureus) T2 - Mycotoxins* *Not listed under CDC Category B agents

Food or Water Borne Pathogens

Salmonella species

Shigella dysenteria

Escherichia coli 0157:H7

Vibrio cholerae

Cryptosporidum parvuus

Q fever

First described in Australia and called Q fever because the causative agent was unknown.

Epidemiology/Microbiology

Q fever is caused by Rickettsia , *Coxiella burnetti* is a world wide zoonosis (44,47,48). The most common reservoirs are cattle, sheep and goats. Other natural reservoirs are dogs, cats and birds. The infected animals do not develop the disease but shed large numbers of organisms in body fluids (milk, urine, and feces) and especially large numbers in the placenta. Humans acquire the disease by inhalation of contaminated aerosol. Q fever as a febrile illness with an atypical pneumonia can resemble mycoplasma, Legionnaire's Disease, Chlamydia pneumonia, psittacosis and Hantavirus infection. More rapidly progressive cases may resemble tularemia or plague. The organism is resistant to heat and desication and highly infectious by aerosol route. A single inhaled organism is capable of producing clinical illness. C. burnetti could be used as an incapacitating biological warfare agent and the disease would be similar to that occurring naturally.

Diagnosis -

The incubation period is 2 - 14 days, varies according to number of organisms inhaled. The disease presents as a self limiting acute febrile illness with headaches, fatigue and myalgias. Pneumonia, manifested by abnormal chest x-ray occurs in 50% of patients and acute hepatitis develops in 33% of patients. Culture negative endocarditis, chronic hepatitis, aseptic meningitis, encephalitis, and osteomyelitis are uncommon complications of Q fever.

Isolation of the organism is difficult. Antibody assay (IFA and ELISA and complement fixation tests) are available at reference laboratories. IgM antibodies may be detected by ELISA as early as the second week of illness and are diagnostic. Complement fixation test, the most commonly available serological test, is relatively insensitive.

Management -

All suspected cases of Q fever should be treated to reduce the risk of complications. Tetracycline or doxycycline or erythromycin for 5 - 7 days are the treatment of choice for Q fever. Azithromycin and Clarithromycin would be expected to be effective, although they have not been tested. Ciprofloxacin and other

quinolones are active in vitro and should be used in patients unable to take the other agents. For endocarditis, tetracycline or doxycycline given in combination with TMP/SMX or rifampin for 12 months or longer has been successful in some cases. Valve replacement is often required for a cure.

Chemoprophylaxis with tetracycline or doxycycline for 5 - 7 days is effective if started 8 - 12 days post exposure. However, if given immediately (1-7 days) after exposure, chemoprophylaxis is not effective and may only prolong the onset of disease.

A formalin inactivated whole cell vaccine is licensed in Australia and available for at-risk personnel on an investigational basis in the United States. A single dose provides complete protection against naturally occurring Q fever and greater than 95% protection against aerosol exposure within 3 weeks. Protection lasts for at least 5 years. The vaccine may cause local induration, sterile abscess and even necrosis at the inoculation site in immune individuals. An intradermal skin test using 0.02 mg of specific formalin - killed whale cell vaccine is required to detect presensitized or immune individuals. A live attenuated vaccine (Strain M44) has been used in the former USSR. There is no person- to- person transmission of Q fever. Standard precautions are recommended for health care workers taking care of patients with suspicion or diagnosis of Q fever.

Brucellosis

Also called undulant fever, Mediterranean Fever, Malta Fever

Epidemiology and Microbiology

Brucellosis is a zoonotic disease caused by infection with one of the six species of Brucellae, a group of facultative intracellular gram negative coccobacilli (36,44,49). The natural reservoir is herbivores like goats, sheep, cattle and pigs. Four species, *B melitensis* (goat), *B. abortus* (cattle), *B. suis* (pig), and *B canis* (dog) are pathogenic in humans. Human infection occurs by ingestion of raw infected meat or milk, inhalation of contaminated aerosols or through skin conduct. Brucellosis is highly infective by the aerosol route, with as few as 10 - 100 bacteria sufficient to cause disease in humans. *Brucella* sp. are stable to environmental conditions and there is a long persistence in wet ground or food. These features make them potential agents of bioterrorism. The disease is relatively prolonged, incapacitating, and disabling in its natural form. Intentional large aerosol doses may shorten the incubation period and increase the clinical attack rate. However, mortality rate (5% of untreated cases) is low with rare deaths caused by endocarditis or meningitis. Brucellosis became the first agent weaponized by the United States at Pine Bluff Arsenal in 1954, when its biological weapons program was active. Human brucellum is an uncommon disease in the United States. The annual incidence is 0.5 cases per 100,000 population. Most cases occur in abattior and veterinary workers or are associated with the ingestion of unpasteurized dairy products. The disease is still highly endemic in the southwest Area (128,000 cases per 100,00 population in some areas of Kuwait). This represents a hazard to military personnel in those areas.

Diagnosis

The usual incubation period is 8 - 14 days but may be longer. Brucellosis presents as a nonspecific febrile illness with headache, fatigue, myalgias, chills, sweats and cough. Lumbar pain and tenderness can occur in up to 60% of cases. GI symptoms - anorexia, nausea, vomiting, diarrhea and constipation occur in up to 70% of adult cases, less frequently in children. Hepatosplenomegaly is seen in 45 - 63% of cases. The significant sequaelae include various osteoarticular infections of the axial skeleton, peripheral arthritis, granulomatous hepatitis, meningitis, encephalitis, peripheral neuropathy, meningovascular syndrome, optic neuritis, infective endocarditis, anemia, thrombocytopenia and leukopenia.

Blood cultures are positive in 15 - 70% and bone marrow cultures in 92% of cases during the acute febrile phase of illness. A biphasic culture method (Castaneda bottle) may improve the isolation rate form blood. Since it may take longer to grow Brucella species, the laboratory must be notified to extend the standard incubation time of 5 - 7 days. If a community laboratory (Level A) observes tiny, faintly staining gram negative coccobacilli with slow growing oxidase positive colonies on sheep blood, all plates and bottles should be placed in a biological safety cabinet. They should be appropriately packaged and shipped to a Level B or C laboratory. Confirmation in laboratories cases can be done by biochemical, slide agglutination or phage lysis tests.

The diagnosis of brucellosis is frequently made by serological tests. Acute and convalescent phase serum should be collected 3 - 4 weeks apart. A serum agglutination test (SAT) is available to detect both IgM and IgG antibodies. A titer of 1:160 or greater in a single specimen is considered indicative of active disease. ELISA and PCR methods are becoming more widely available.

Management

The United States military recommends doxycycline (100 mg Q12 hr) plus rifampin (900 mg a day) for six weeks. Doxycycline for 6 weeks plus streptomycin for 2 - 3 weeks is an acceptable alternative. TMP/SMX for 4 - 6 weeks is less effective Long term therapy with a combination of a tetracycline, rifampin and an aminoglycoside is recommended for patients with meningoencephalitis or endocarditis. Valve replacement and surgical intervention for other forms of localized disease may be needed. Chemoprophylaxis is not generally recommended. For a high risk exposure to veterinary vaccine, inadvertent exposure in a laboratory or exposure in biological warfare context, a 3 - 6 weeks course of therapy with the agents used for treatment should be considered for prophylaxis.

Live animal vaccines are used widely and have eliminated brucellosis from most domestic animal herds in the US. No licensed human vaccine is available in the United States. A variant of *Brucella abortus*, S19-BA has been used in the former USSR. Efficacy is limited and annual revaccination is needed. A similar vaccine is available in China. Since brucellosis is not generally transmissible from person-to-person, standard precautions are adequate in managing patients. BSL-3 practices should be used for handling suspected Brucella cultures in the laboratory because of the danger of inhalation.

Glanders and Melioidosis

Epidemiology and Microbiology

Caused by *Burkholderia mallei* and *Burkholderia pseudomallei* respectively (44). Both are gram negative bacilli with a "safety pin" appearance on microscopic exam. *Burkholderia mallei*, the causative agent of glander produces disease primarily in horses, mules and donkeys. Human disease is uncommon despite frequent and/or close contact with infected animals. Low concentrations of the organisms and less virulence for humans may be the factors responsible. The acute forms of the disease occur in mules and donkeys resulting in death in 3 to 4 weeks. The chronic form of the disease is more common in horses with lymphadenopathy, multiple skin nodules that ulcerate and drain, along with induration, enlargement and nodularily of regional lymphatics. The later presentation is called tarey. Human cases occur primarily in veterinarians and animal handlers. Infection is acquired from inhalation or contaminated injuries. *B. pseudomallei*, the causative agent of melioidosis is widely distributed in many tropical and subtropical regions. It is endemic in Southeast Asia and Northern Australia. Humans get infected by inhalation or contact with mucous membranes and skin. Melioidosis is one of the most common causes of community acquired septicemia in Northeastern Thailand. This represents a hazard to military personnel in those areas. In humans, the disease ranges from a subclinical infection to overwhelming septicemia with 90% mortality rate with 24 - 48 hours. Chronic and life threatening illness can also occur from reactivation of primary illness.

Aerosols from cultures of *B. mallei* and *B. pseudomallei* are highly infectious to laboratory workers making aerosol spread an efficient way of dissemination. A case of glanders in a military research microbiolgist was reported recently (45). Both of these organisms ave been viewed as potential biological warfare agents.

During World War I glanders was spread deliberately by central powers to infect large numbers of Russian horses and mules. This led to increase in human cases in Russia after World War I. The Japanese infected horses, civilians and prisoners of war with B. mallei at Pin Fang (China) Institute during World War II. The United States studied both agents as possible biological weapons in 1943-1944 but did not weaponize it. The former Soviet Union is believed to have experimented with *B. mallei* and *B. pseudomallei* as bioweapons.

Diagnosis

The incubation period is 10 - 14 days. In the acute forms, both glanders and melioidosis can present as an acute pulmonary infection or as an acute fulminant, rapidly fatal septicemic illness. These are the forms that would be expected in case of their use as bioweapons. Acute infection of the oral, nasal and conjunctival mucosa can cause bloody nasal discharge with septal and turbinate nodules and ulcerations. Systemic invasion can cause a papular or pustular rash that can be mistaken for small pox as well as hepatic, splenic and pulmonary abscesses. Acute forms of the diseases carry a high mortality rate.

The chronic form is characterized by cutaneous and intramuscular abscesses on the legs and arms.

Osteomyelitis, meningitis, and brain abscesses have also been reported.

Gram stain of the exudates show gram negative bacteria with bipolar staining. They stain irregularly with methylene blue or Wright's stain. The organisms can be cultured and identified with standard bacteriological methods.

For *B. mallei*, agglutination and complement fixation tests are available for serological diagnosis. Complement fixation tests are more specific and considered positive if the titer exceeds 1:20. For *B. pseudomallei*, a single titer above 1:160 with a compatible illness suggests active infection.

Management

For localized disease, oral therapy with Amoxicillin /Clavulanate, tetracycline or TMP/SMX for 60 - 150 days is recommended. For severe disease, parenteral therapy with ceftazidime plus TMP/SMX for two weeks followed by oral therapy for six months is recommended. Post exposure chemoprophylaxis may be tried with TMP/SMX. No vaccine is available for human use. Standard precautions should be used for infection control purposes.

Top

Category B - Viral Agents of Bioterrorism

Equine Encephalitis

Mosquito-borne alpha viruses cause Venezuelan equine encephalitis (VEE), Western equine encephalitis virus (WEE), and Eastern Equine Encephalitis (EEE) (44,49). They are similar, share many aspects of epidemiology and transmission and are often difficult to distinguish clinically. Natural infections are acquired by bites of a wide variety of mosquitoes. In natural epidemics severe and often fatal encephalitis in horses, mules, and donkeys precedes human cases. In a biological warfare attack with the virus disseminated as an aerosol, human disease would be a primary event or occur simultaneously with that in equidae. The human infective dose of VEE is 10 - 100 organisms. VEE is a febrile, relatively mild incapacitating illness. Encephalitis develops in a small percentage of patients. EEE and WEE viruses cause encephalitis predominately.

No specific therapy is available. Alpha-interferon and the interferon induce poly-ICLC have proven highly effective as post-exposure prophylaxis in experimental animals. A live attenuated vaccine is available as an investigational new drug. A formalin inactivated vaccine is available for boosting antibody titers in those initially receiving the live attentuated vaccine.

The viruses can be destroyed by heat (80OC for 30 minutes) and standard disinfection. There is no evidence for human-to-human or horse to human transmission. Standard precautions and vector control are adequate infection control procedures while the patient is febrile.

Top

Category B - Biological Toxins

Ricin Toxin

Ricin is a protein cytotoxin derived from the beans of the castor plant (*Ricinus communis*). The castor plant is ubiquitous and the toxin is easy to export. It is stable and highly toxic by several routes of exposure including inhalation (44,48).

Following inhalational exposure, acute onset of fever, chest tightness, cough, dyspnea, nausea and arthralgia occur within 4 - 8 hours. Acute respiratory distress syndrome in 18 - 24 hours is followed by hypoxemia and death in 36 - 72 hours. Ricin antigen can be detected in the serum and respiratory secretions by ELISA. Retrospective diagnosis is provided by antibody testing in acute and convalescent sera.

No specific therapy is available. Gastric lavage and emetics are indicated for ingestion. Being a large molecule, charcoal is not useful for ricin poisoning.

There is no vaccine or prophylactic immunotherapy available for human use. Immunization appears promising in animal models. A protective mask is the best protection against inhalation. Secondary aerosols are not a danger to others and ricin in non volatile. Standard precautions are adequate for health care workers. Hypochloric solution (0.1% sodium hypochloride) inactivates ricin.

Epsilon (Alpha) Toxin

Clostridium perfringens produces 12 toxins (49). One or more of them could be weaponized. The alpha toxin, a highly toxic phospholipase can be lethal when delivered as an aerosol. The toxin would cause vascular leaks and severe respiratory distress. It can also cause thrombocytopenia and liver damage. The toxin can be detected from serum and tissue samples by a specific immunoassay. Bacteria can be cultured easily. There is some data to show that clindamycin or rifampin may decrease the toxin production by *C. perfringens*. However, there is no specific prophylaxis against most of the *C perfringens* toxins. Some toxids are available for enteritis necroticans in humans. Veterinary toxids are widely used.

Enterotoxin B

These toxins are proteins with a molecular weight of 23,000 - 29,000 daltons (44,49). *Staphylococcus aureus* produces a number of exotoxins and since they normally exert their effect on the GI tract thy are called Enterotoxins. They are also called Pyrogenic toxins because they cause fever. Staphylococcus Enterotoxin B (SEB) is a pyrogenic toxin that commonly causes food poisoning from improperly handled or refrigerated food. The effect of the inhaled SEB is markedly different. Symptoms occur at a very low inhaled dose (< 1/100th of the dose to cause GI symptoms). The diseases begins rapidly within 1 - 12 hours after ingestion with sudden

onset of fever, chills, headache, myalgia and a nonproductive cough. Pulmonary edema occurs in severe cases. GI symptoms can occur concomitantly due to inadvertent swallowing of the toxin after inhalatione US Bioweapons program possessed prior to its termination in 1969.

There is no specific therapy available. Experimental immunization has been reported. No human vaccine is available. A candidate vaccine is in advanced development. Secondary aerosols are not a hazard and SEB does not pass through intact skin. Standard precautions for health care workers are recommended.

T-2 Mycotoxins

Trichothecene mycotoxins are a group of more than 40 toxins produced by common molds like Fusarium, Myrotecium, Trichoderma, Stachybotrys and other filamentous fungi. They are extremely stable in the environment and the only class of biological toxins that cause skin damage. Usual hypochlorite solution does not inactivate these toxins. They retain bioactivity even after autoclaving. Skin exposure causes pain, pruritus, reduess, vesicles, necrosis and sloughing. Severe irritant effects are seen on the respiratory tract, GI tract and eyes on contact. Severe intoxication results in shock and death. Diagnosis should be suspected if an aerosol attack occurs in the form of "yellow rain" with contamination of the clothes and the environment by pigmented oily fluids.

Treatment is supportive only. Soap and water washing can prevent or significantly reduce dermal toxicity if done within 1 - 6 hours. Superactivated charcoal should be used for oral intoxication.

No prophylactic chemotherapy or immunotherapy is available in the field . Exposure during an attack should be prevented by mask and clothing. Secondary aerosols are not a hazard. Contact with contaminated skin and contaminated clothing can produce secondary dermal exposures. Until decontamination is accomplished, contact precautions are needed. Subsequently, standard precautions are recommended for health care workers. Environmental decontamination requires 1% sodium hypochloride with 0.1% NAOH for 1 hour contact time.

Other Toxins With Potential for Bioterrorism

- Tetanus toxin from *C. tetani*
- Saxitoxin - a dinoflagellate toxin responsible for paralytic shellfish poisoning
- Tetrodotoxin - A potent neurotoxin produced by fish, salamanders, frogs, octopus, starfish and mollusks
- Toxins from blue-green algae

Class C Agents for Bioterroism

The agents in this group with the third highest priority include emerging pathogens that could be engineered for mass dissemination. The characteristics that render them amenable to bioterrorism are -

Availability
Ease of production and dissemination
Potential for high morbidity and mortality and major health impact

The agents included in this category are:
Nipah virus
Hantavirus - discussed in the presentation on viral hemorrhagic fevers
Tick borne hemorrhagic fever viruses
Tick borne encephalitis viruses
Yellow fever - discussed in the presentation on viral hemorrhagic fevers
Multidrug resistant tuberculosis

Nipah virus

The 1998 - 1999 outbreak in Malaysia caused 1 million deaths in swine and encephalitis in 265 humans. The disease was eradicated from swine but is still likely to be present in fruit bats. Humans contracted Nipah virus by coming into direct contact with swine. Human-to-human transmission has not been documented. Mortality rate is about 40%. No cases have been documented in the United States.

Tick borne complex of viruses that cause encephalitis in humans include Far Eastern, Central European, Kyasanur Forest, Louping ill, Powassan and probably Negishi (50). Tick borne hemorrhagic fevers include Crimean-Congo hemorrhagic fever, Omsk hemorrhage fever and Kyasanur Forest disease (51).

Preparedness for the Public Health and Medical Communities

The CDC was designated by the Department of Health and Human Services to prepare the United States Public Health system to respond to a bioterrorism event (53). To enhance the preparedness at local and state levels, the CDC funded co-operative agreements with states and several large cities (54). Five areas were emphasized for the first 3 years (1999-2001) of this program -

1. Preparedness, planning and readiness assessment
2. Surveillance and epidemiology capacity
3. Biological laboratory capacity
4. Chemical laboratory capacity
5. Health alert network and training

The United States Food and Drug Administrations is participating in an interagency group preparing for response in a civilian emergency (55) The USAMRIID maintains an aeromedical isolation team to minimize the risk of transmission from the troops to air crews, caregivers and civilians (56).

Traditional first responders like firefighters and law enforcement officers are the most likely to respond to an announced attack, whereas physicians and other health care providers would be most likely to uncover an

unannounced attack. In either case, the medical community at large will be responsible for diagnosis and management of diseases caused by biological and chemical weapons. ACP/ASIM has published a useful pocket guide to bioterrorism identification (Appendix C). The Association for Professionals in Infection Control and Epidemiology (APIC) in cooperation with the CDC has prepared a Bioterrorism Readiness Plan to serve as a reference document and a template to facilitate preparation of bioterrorism readiness plans for individual institutions (57). National Association of Counties conducted a survey of county Public Health directors (58). A significant number of responding counties (300 counties in 36 states) reported less than optimal levels of preparedness for biological and chemical warfare and for policies and procedures to enforce a quarantine. Among the reasons cited for unpreparedness were insufficient funding, insufficient work force and insufficient communications networks. In most cities, large health care institutions have disaster plans and various types of task forces with "experts" in different areas in place. However, they need to be updated and modified to include new information on biological and chemical weapons.

In addition to being able to recognize and manage diseases associated with bioterrorism events, health care providers will need to stay abreast of new developments. Use of Automated Ambulatory Care Encounter Records for Detection of Acute Illness Clusters, including Potential Bioterrorism Events, has been discussed in detail in a recent publication (59). The same issue of *Emerging Infectious Diseases* (August, 2002) has a review on the activity of humoral immunity against several biological agents and discusses the use of passive antibody administration (Immediate Immunity) as a specific defense against biological weapons (60).

Various models and estimates of the economic impact of bioterrorism attacks have been published. Rapid implementation of a post-attack prophylaxis program is the single most important means of reducing the huge economic impact (61). The model proposed by Kaufamnn et al. provides economic justification for preparedness measures.

We would like to conclude this discussion with a quote

> **"Modern adventurers like to up the ante, but even the most extreme sports wouldn't produce the adrenaline of a race against pandemic influenza or a cloud of anthrax at the Super Bowl. In the field of Infectious Diseases, reality is stranger than anything a writer could dream up. The most menacing bioterroist is Mother Nature herself."**
> ***Secret Agents: The Menace of Emerging Infections*, by Madeline Drexler, John Henry Press, 2002**

In the end, we wish to express our gratitude to Sarah Starks and Nancy Mutzbauer at the Southern Illinois University School of Medicine. Their assistance in collecting the most recent literature and helping convert thoughts and rough drafts into a presentable review was invaluable.

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